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Mr.
C. Russ Rutledge
Center for Drug Evaluation (HFD-325)
Food and Drug Administration
5600 Fishers Lane, rm 1745

MD 20857 Rockville/USA

Singen, 19. März 1999/Rg-bu

Draft Guidance for Industry: Investigating Out of Specification (OOS) Test Resultats for Pharmaceutical Production

Dear Mr. Rutledge,

thank you once again for your and your offices kind cooperation regarding our workshop.

Attached please find our announced comments. Please accept our apology for the delay. We hope this will not prevent you from taking our comments into consideration when filing the final draft.

Yours sincerely

Dr. Bernd Renger
(dep. chairman)

Enclosure:
- Comments and Suggestions

Copy to: Dockets Management Branch (HFA-305), Food and Drug Administration, 5230 Fishers Lane., rm. 1061, MD 20857 Rockville/USA

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Comments and Suggestions Regarding the FDA/CDER Draft Guidance "Investigating Out of Specification (OOS) Test Results in Pharmaceutical Production"

On Tuesday 23rd February 1999, a group of experts invited by the German Pharmaceutical Society, Expert Group Pharmaceutical Analysis / Quality control, representing the pharmaceutical industry, the pharmacopoeial authorities and inspectorates and the universities met at a workshop on "The variability of analytical test procedures, specification limits and out-of-specification (OOS) test results".

The goal of the meeting was to formulate comments on the "Guidance for Industry – Investigating Out of Specification Results for Pharmaceutical Production" draft distributed for Comment purposes by the FDA in September 1998.

Comments are made on the following points:

1. Introduction

" ... This guidance for industry provides the Agency's current thinking on how to evaluate suspect, or out of specification (OOS), test results. For purposes of this document, the term OOS results includes all suspect results that fall outside the specifications or acceptance criteria established in new drug applications, official compendia, or by the manufacturer...."

Specifications are an integral part of applications. In certain justified cases they may vary from those given in compendia. Generally, formulated product specifications in the USP (e.g. dissolution) may not be applicable and may be replaced by more scientifically based specifications defined by the manufacturer. To avoid any misinterpretation, the reference to official compendia and/or drug applications should be deleted.

2. The area of validity should be defined more clearly

"...This guidance applies to laboratory testing during the manufacture ..."

The guideline should apply exclusively to:

- Finished products,
- APIs,
- Excipients

It should not apply to:

- In-process controls
- Reagents, chemicals and intermediates used in the synthesis of active pharmaceutical ingredients, other than the active substance itself
- Internal (unofficial) narrower specifications

To emphasize this, it was suggested by the participants, that *"during the manufacture"* should be deleted from the text.

OOS results of IPC tests that are used to control and adjust production parameters should trigger the stipulated actions. If IPC results after such control actions are still OOS, investigation on a lower formalized level should be started.

In addition it should be clearly mentioned that the guideline should not apply to stability testing when OOS results are expected (e.g. stress testing, accelerated degradation studies).

3. Testing (Chap. IV B)

"...The number of retests to be performed on a sample should be specified in advance by the firm in the SOP..."

It is not meaningful to specify a general number of retests to be performed on a sample in a SOP.

The possibility should in fact be given in each individual case and independent of the test procedure used to predetermine and document the number of tests to be performed prior to carrying out a retest, in a written, approved protocol.

"...Retesting should be performed by an analyst other than the one who performed the original test..."

The demand for a second analyst for such purposes is not always a practical solution and should be deleted.

4. Averaging (Chap. IV B)

The participants unanimously welcomed the clear statement towards scientific sound parallel or replicate measurements given in the draft guidance paper. Individual values should not be matched against specifications, only the (reportable) result.

It was therefore suggested that it be emphasized that the following paragraphs of the guidance paper do not refer to replicate measurements but to averages of (reportable) results:

"...Relying on test data averaging in such a case can be particularly misleading. For example, in an assay with a given range of 90 to 110 percent, test results of 89 percent, 89 percent, and 92 percent would produce an average of 90 percent even though two of the assay values represent failing results.

To use averaged results for assay reporting, all test results should conform to specifications. Although the above average of 90 percent may be useful in terms of an overall assessment of process capabilities, the individual assay results indicate nonconformance because two of the three results are outside of the range..."

It was agreed that in general batches may only be released – without any further analyses – if all reportable results are within specification.

From a scientific point of view the following alternative approach may be acceptable:

In principle it is statistically possible for a random sample to produce a result out of specification even though the batch itself may conform to specification. If in the case of a triplicate assay 1 result is OOS but 2 results are within, a further triplicate assay should be carried out. Should then none of the 3 results be OOS, the batch can be released.

In the case that analytical results from content uniformity tests are averaged to an assay result (an approach that is much encouraged by the group of experts *[Pharm. Forum Volume 24, Number 1]*), any individual assay result must comply with the content uniformity specification limits and not with the narrower assay limits. The averaged result then has to comply with the assay specifications.

"...A low assay value may also trigger concerns that the batch was not formulated properly because the batch must be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient (21 CFR 211.101(a))..."

In Europe, generally narrower (95% - 105%) release limits than in USA are expected for the content. Hence, borderline results should not automatically lead to an OOS procedure being invoked (this is in fact contradictory to the area of validity as defined) as this would in turn result in an even narrower "virtual" specification. This, from both the analytical and statistical points of view, is not meaningful and would trigger unnecessary failure investigations.

The additional suggestion to discuss a 95 % confidence interval (PDA comments) are not considered useful.

5. Outliers (Chap. IV B)

Outlier tests should as a rule only be used to identify results showing an extreme deviation from other results obtained that cannot be explained by the procedure's inherent variability. In the case of physical / chemical analyses, there is no legitimization for eliminating results simply because they have been identified as outliers. However, once one value has been identified as not being explainable simply on the basis of the procedure's variability, all further lab investigations should focus on this value. If it can be related to an obvious lab error or if there is a "preponderance of evidence" that a lab error or failure during analysis has caused this value, it may be invalidated and substituted by a retesting value and hence no longer regarded as an outlier.

In any case, the result obtained from an outlier test is dependent on the type of model used in the determination.

6. Risk analysis

The risk arising from a certain parameter of a particular batch not conforming with specification (due to an OOS result confirmed in the laboratory as a consequence of an informal investigation) should be assessed and taken into account during the following failure investigation process and should in fact determine the extent of the investigation (the investigation of an unknown contaminant should involve a more extensive investigation than, say, a slight discoloration!). It must be allowed that the company's experts decide on the basis of professional judgement to what extent an investigation is meaningful and adequate.

7. Laboratory Phase of an Investigation (Chap. IV B)

"... A number of practices are used during the laboratory phase of an investigation. These include: (1) retesting a portion of the original sample, (2) testing a specimen from the collection of a new sample from the batch, (3) resampling testing data, and (4) using outlier testing. .."

It should be stated that the responsibility at the laboratory level is in hands of the Laboratory Management. There is no need QA departments to become involved.

If an OOS result is confirmed, i.e. a batch is suspected of not complying with specification, a formalized failure investigation including QA, QC and production departments should be started.

8. Glossary

A glossary should be added to the Guidance Note so that everyone is quite clear as to what certain terms mean (e.g. test result, replicate, result, individual test result).

Prof. Hamacher
chairman

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dep. chairman

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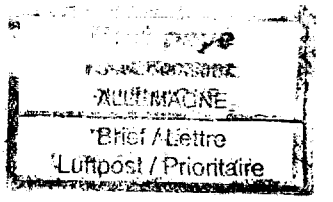

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